

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/110620/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

John, Ann, McGregor, Joanna, Jones, Ian ORCID: <https://orcid.org/0000-0001-5821-5889>, Lee, Sze Chim, Walters, James T.R. ORCID: <https://orcid.org/0000-0002-6980-4053>, Owen, Michael J. ORCID: <https://orcid.org/0000-0003-4798-0862>, O'Donovan, Michael ORCID: <https://orcid.org/0000-0001-7073-2379>, Banos, Marcos Del Pozo, Berridge, Damon and Lloyd, Keith 2018. Premature mortality among people with severe mental illness - new evidence from linked primary care data. *Schizophrenia Research* 199 , pp. 154-162.
10.1016/j.schres.2018.04.009 file

Publishers page: <http://dx.doi.org/10.1016/j.schres.2018.04.009>
<<http://dx.doi.org/10.1016/j.schres.2018.04.009>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies.

See

<http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.





Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Premature mortality among people with severe mental illness – New evidence from linked primary care data

Ann John^{a,b,*}, Joanna McGregor^{a,b}, Ian Jones^{b,c}, Sze Chim Lee^{a,b}, James T.R. Walters^{b,c}, Michael J. Owen^{b,c}, Michael O'Donovan^{b,c}, Marcos DelPozo-Banos^{a,b}, Damon Berridge^a, Keith Lloyd^{a,b}

^a Farr Institute, Swansea University Medical School, Singleton Park, Swansea SA2 8PP, UK

^b National Centre for Mental Health, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff CF24 4HQ, UK

^c MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Hadyn Ellis Building, Maindy Road, Cathays, Cardiff CF24 4HQ, UK

ARTICLE INFO

Article history:

Received 18 December 2017

Received in revised form 19 March 2018

Accepted 3 April 2018

Available online xxx

Keywords:

Mortality

Primary care

Severe mental illness

Schizophrenia

Bipolar disorder

ABSTRACT

Studies assessing premature mortality in people with severe mental illness (SMI) are usually based in one setting, hospital (secondary care inpatients and/or outpatients) or community (primary care). This may lead to ascertainment bias. This study aimed to estimate standardised mortality ratios (SMRs) for all-cause and cause-specific mortality in people with SMI drawn from linked primary and secondary care populations compared to the general population. SMRs were calculated using the indirect method for a United Kingdom population of almost four million between 2004 and 2013. The all-cause SMR was higher in the cohort identified from secondary care hospital admissions (SMR: 2.9; 95% CI: 2.8–3.0) than from primary care (SMR: 2.2; 95% CI: 2.1–2.3) when compared to the general population. The SMR for the combined cohort was 2.6 (95% CI: 2.5–2.6). Cause specific SMRs in the combined cohort were particularly elevated in those with SMI relative to the general population for ill-defined and unknown causes, suicide, substance abuse, Parkinson's disease, accidents, dementia, infections and respiratory disorders (particularly pneumonia), and Alzheimer's disease. Solely hospital admission based studies, which have dominated the literature hitherto, somewhat over-estimate premature mortality in those with SMI. People with SMI are more likely to die by ill-defined and unknown causes, suicide and other less common and often under-reported causes. Comprehensive characterisation of mortality is important to inform policy and practice and to discriminate settings to allow for proportionate interventions to address this health injustice.

© 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The increased risk of premature death in people with severe mental illness (SMI) compared to the general population is well established (Brown et al., 2000; Hayes et al., 2017; Osborn et al., 2006). Studies to date have mostly been based in one setting, hospital (secondary care inpatient and/or outpatients) or community (primary care), rather than using linked population level data, and have consistently reported a two to three fold increase in all-cause mortality ratios. This corresponds to a reduction in life expectancy of 10–20 years for those with SMI – a clear health injustice. It is often assumed that studies based in the secondary healthcare setting are unlikely to bias findings on this mortality gap since most people with SMIs are likely to have accessed secondary

care (Jayatilleke et al., 2017). However, this assumption is worth exploring. Mortality risk may be over or under estimated since more serious and vulnerable cases will be over-represented in hospital inpatient and outpatient settings (Amaddeo et al., 1995; Carney et al., 2006; Copeland et al., 2009; Crump et al., 2013; Jayatilleke et al., 2017; Kessler et al., 2005) and possibly under-represented in community/primary care settings (Hayes et al., 2017; McDermott et al., 2005; Osborn et al., 2007; Osborn et al., 2006). Here, we report what is to our knowledge the first analysis of mortality risk using person level linked hospital and primary care data to explore the extent to which ascertainment bias has played a part in risk estimates from previous studies based in one setting alone (hospital or primary care).

Some causes associated with this premature mortality are well documented. Suicide risk in those with SMI is highly associated with acute psychotic episodes and psychiatric hospitalisation, peaking during admission and shortly after discharge (Appleby et al., 2001; Nordentoft et al., 2013). People with SMI often have poor physical health and greater levels of obesity than the general population (Leucht et al., 2007). Deaths from cardiovascular, metabolic and respiratory diseases are common and account for most of the excess mortality from natural

Abbreviations: CI, Confidence Interval; GPD, General Practice Database; ICD, International Classification of Diseases; ONS, Office for National Statistics; PEDW, Patient Episode Database for Wales; SAIL, Secure Anonymised Information Linkage; SMI, severe mental illness; SMR, standardised mortality ratios; WDS, Welsh Demographic Service.

* Corresponding author at: Swansea University Medical School, ILS2, Swansea University, Swansea SA2 8PP, UK.

E-mail address: a.john@swansea.ac.uk (A. John).

<https://doi.org/10.1016/j.schres.2018.04.009>

0920-9964/© 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article as: John, A., et al., Premature mortality among people with severe mental illness – New evidence from linked primary care data, Schizophr. Res. (2018), <https://doi.org/10.1016/j.schres.2018.04.009>

causes in both inpatient and community settings (Bushe et al., 2010; Copeland et al., 2009; Correll et al., 2017; Jayatilleke et al., 2017; Olfson et al., 2015; Osborn et al., 2007). A number of physical comorbidities were particularly over-represented in a recent study using a large primary care database (Olfson et al., 2015). These included Parkinson's disease and some disorders of the liver and the digestive system, with diseases such as epilepsy, diabetes, and respiratory disorders notably elevated in comparison to the general population. Many studies only report on common causes of natural deaths, while less common causes are under-reported, often due to insufficient sample sizes. Hence, in the present study we aimed to report a comprehensive assessment of mortality in people with SMI drawn from primary and secondary care populations compared to the general population.

2. Materials and methods

2.1. Design

A retrospective electronic cohort study.

2.2. Study population and setting

The whole population of 3.9 million individuals in Wales, 2004–2013, was included in the study. SMI diagnoses were divided into three groups based on the diagnostic categories in the International Classification of Diseases (ICD) version 10 and Read Codes version 2: 1) schizophrenia, schizotypal and delusional disorders; 2) bipolar disorder and other mood related disorders; 3) other severe mental illness (Read Codes only relating to 'other non-organic psychoses'). Supplementary Table 1 lists study related ICD-10 codes.

2.3. Data source

The Farr Institute's Secure Anonymised Information Linkage (SAIL) databank (www.saildatabank.com) was used in the study. SAIL is an expanding data repository (around 3 billion records) of anonymised person based linkable data from healthcare and public settings to support research. Policies, processes, structures and controls to manage and maintain this databank have been described elsewhere (Ford et al., 2009; Lyons et al., 2009). We utilised the following datasets in our study:

1. The Office for National Statistics (ONS) deaths register, which houses nationwide information on cause covering the whole population of Wales.
2. General Practice Database (GPD), which contains diagnoses, symptoms, investigations, prescribed medication, referrals, coded hospital contacts and test results. At time of analysis 71% (338/474) of all general practices in Wales were supplying SAIL with their data.
3. Patient Episode Database for Wales (PEDW), an NHS Wales hospital admissions dataset comprising clinical information of all hospital admissions (inpatient and day cases) covering the whole population of Wales.
4. Welsh Demographic Service (WDS) an administrative register of all individuals in Wales that use NHS services, which includes anonymised demographics and practice registration history.

2.4. Measures

We used ICD-10 codes for SMI (Supplementary Table 1) to interrogate PEDW for both planned and emergency admissions identifying SMI cases as the principal discharge diagnosis for hospitalisation as done in previous studies assessing premature mortality (Ford et al., 2009). We used Read Code version 2 to identify cases of SMI in the GPD. Diagnostic codes used to identify people with SMI in the GPD have been previously validated (Economou et al., 2012; Lloyd et al., 2015). Diagnoses related to SMI, number of deaths and cause of deaths

were extracted within the study period (01/01/2004–31/12/2013). ICD-10 codes were used to classify cause of death and were grouped into main categories. We further categorised causes of death into natural and unnatural (accidents, assault, suicide, self-harm and undetermined intent). Supplementary Table 2 tabulates categories and sub-categories of causes of death as well as the corresponding ICD-10 codes used in the study.

2.5. Analysis

We utilised the WDS to collect demographic information, such as week of birth and sex. The age of each individual was calculated at the midpoint of the follow-up period and described according to the following categories: under 45, 45–64, 65–84 and 85 or above years in accordance with other studies of this type (Hoang et al., 2011).

Standardised mortality ratios (SMRs) were calculated using the indirect method with the WDS population as the standard population. We estimated SMRs for four sets of patient cohorts identified as follows:

- a) Primary care cohort: patients with a SMI diagnosis from the GPD within the study period using a previously validated algorithm (Economou et al., 2012; Lloyd et al., 2015);
- b) Primary care cohort with no hospital admissions: patients with at least one GP diagnosis related to SMI but without subsequent inpatient diagnosis for the same disorder within the study period;
- c) Secondary care cohort: patients with a principal diagnosis from PEDW (inpatient diagnosis) related to SMI within the study period; and
- d) Combined cohort: combining the primary (a) and secondary (c) cohorts.

The start date of the follow-up period was defined as the date of the first inpatient or GP SMI related diagnoses within the study period (01/01/2004–31/12/2013). An individual was included in the cohort once only. The end date was the death date, the end of the study period (31/12/2013) or the last end date of registration in the WDS within the study period, whichever came first. For the combined primary and secondary cohort (combined cohort), the start date of the follow-up period was the earlier date of either the GP or inpatient diagnosis. For individuals with no SMI related diagnosis, the start date of the follow-up period was the beginning of the study period (01/01/2004) and the end date was the death date or the end of the study period, whichever came first.

All-cause and cause-specific mortality rates were calculated using the person years at risk corresponding to the follow-up periods (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010; Ressing et al., 2010). SMRs were calculated by dividing the observed numbers of deaths in the SMI cohorts (primary care, primary care without hospital admission, secondary care and combined cohort) by the expected number of deaths derived from the age (5-year age bands) and sex-matched all-cause and cause-specific mortality rates found in the whole of Wales. SMRs for causes with a small number of observed deaths (e.g., diseases of the eye and ear) were not reported (refer to Supplementary Table 2).

We further characterised the four cohorts by age, sex, diagnostic category and stratified by underlying causes of death. To calculate SMRs for the cause of death of people within SMI categories, we used the rates from the corresponding specific causes within the population of Wales. We conducted further additional analyses to make comparisons between SMRs for specific causes of death between cohorts sourced from primary care and secondary care settings.

Data in the SAIL databank were interrogated using structured query language (SQL DB2). All confidence intervals (CIs) of the SMRs were two-tailed mid-*p* exact CIs, assuming Poisson distribution for the observed deaths, and were calculated as previously described (Rothman

and Boice Jr, 1979). CIs for proportions and percentages were estimated by the Wilson score method with continuity correction (Newcombe, 1998).

2.6. Ethical approval

The use of data in the SAIL databank for this study have the required permissions from the SAILindependent Information Governance Review Panel, which includes representatives with a variety of expertise from different organisations: BMA, NRES, Involving People, NHS Wales Informatics Service and Public Health Wales NHS Trust. This study forms part of the “PsyCymru study” (Lloyd et al., 2015) ethically approved by Wales REC 3 (14/WA/1136).

3. Results

3.1. Participants, number of deaths and demographics

The standard population was the whole population of Wales in WDS over the ten-year observation period. This consisted of 3.9 million people providing 35.3 million years of person time with 377,511 deaths observed. In the primary care cohort sourced from GPD, there were 2720 deaths over 112,316 person years, provided by 21,589 individuals with a SMI diagnosis. Of these, 37.8% (8163/21,589) also had hospital admissions and were present in the secondary care cohort. For the remaining patients within the primary care cohort (i.e., those seen in primary care and/or with recorded out-patient appointments where no hospitalisation for the same SMI occurred) we observed 1753 deaths out of 62,459 person years provided by 13,426 individuals. In the secondary care cohort, there were 2956 deaths within the 83,300 person years contributed by 16,371 individuals diagnosed with a SMI with hospital admissions.

In the combined cohort, there were 4709 deaths out of 153,263 person years, contributed by 29,797 individuals who had received a diagnosis of SMI recorded in either primary care or secondary care. For this combined cohort, 27.5% (8208/29,797) were sourced from secondary care cohort (hospital admissions only), 45.1% (13,426/29,797) were from the primary care cohort (GP and recorded out-patients), and 27.4% (8163/29,797) were from both primary and secondary cohorts, i.e., had a SMI diagnosis recorded in primary care and also had a hospital admission.

The distribution in terms of demographics (sex, age, deprivation) across each cohort is shown in Supplementary Table 3. Sex was evenly divided (50/50). Almost half of the cases were under 45 years (40.8%–47.3%) and 26.2%–26.8% resided in the most deprived quintile at the start of follow-up (ranges across all cohorts). Those in the hospital admissions secondary care cohort included lower percentages of under 45 year olds and those from the least deprived quintile compared to all the other cohorts. Over a third (>36%) had bipolar disorder, Schizophrenia ranged from 46.9% to 62.1% across settings with other SMI accounting for the remainder.

3.2. All-cause SMRs for different cohort ascertainment methods

The mortality ratios (and CIs) for cohorts ascertained from the different settings are illustrated in the forest plot (Fig. 1). We found mortality ratios to be higher for the secondary care hospital admissions cohort (2.9; 95% CI: 2.8–3.0) than for the primary care cohort (2.2; 95% CI: 2.1–2.3), as well as the primary care cohort without hospital admission (2.3; 95% CI: 2.2–2.4) when compared to the general population of Wales. The all-cause SMR was 2.6 (95% CI: 2.5–2.6) for the combined cohort.

3.3. All-cause SMRs in the combined cohort

The range of age at death in the combined cohort was 15–108 years old; with the mean age at death being 72.7 years old. The breakdown by age groups of age at death was: 9.8% (461/4709) were under 45 years; 21.2% (996/4709) aged 45–64 years; 47.1% (2216/4709) aged 65–84 years; and 22.0% (1036/4709) of deaths aged 85 years and over.

The all-cause SMRs for all those with SMI and for SMI categories by age and sex in the combined cohort are summarised in Table 1. Males (SMR: 3.0; 95% CI: 2.9–3.2) had higher all-cause SMR than females (SMR: 2.3; 95% CI: 2.3–2.4). Higher ratios were observed in the younger age groups. Ratios for schizophrenia related disorders were higher (SMR: 2.7; 95% CI: 2.6–2.8) than for people with bipolar and other mood related psychotic disorders (SMR: 2.2; 95% CI: 2.1–2.3).

3.4. Cause-specific mortality in the combined cohort

Fig. 2 illustrates the proportion of deaths by major underlying causes and the corresponding SMRs for the combined cohort. Nearly two-thirds of all the deaths were from circulatory, respiratory disorders

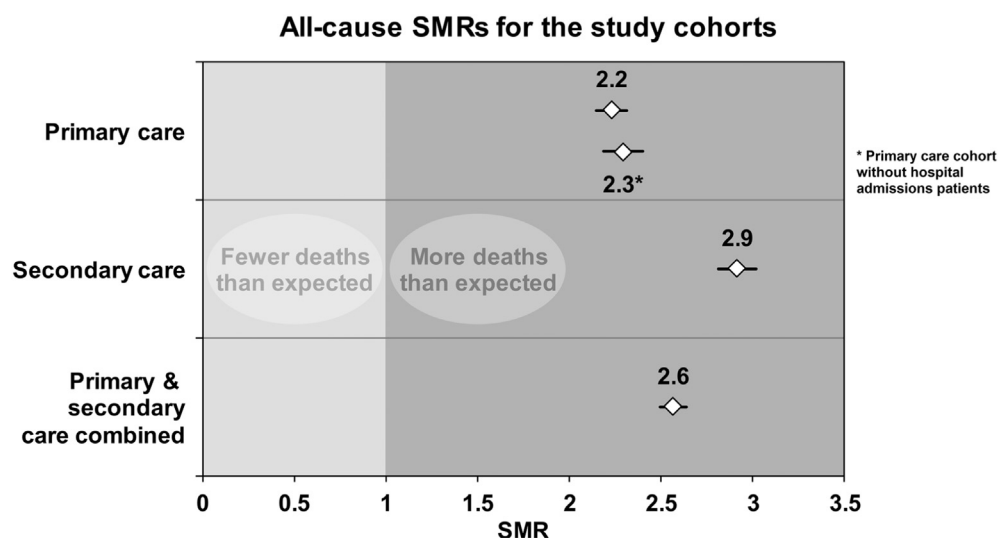


Fig. 1. Forest plot showing all-cause SMR (white diamonds and the associated number labels) for people diagnosed with SMI by three cohort ascertainment methods. SMR less than one (light shaded region) represents observed deaths fewer than the expected deaths derived from the general population while SMR greater than one (dark shaded region) represents observed deaths greater than the expected deaths. Error bars: 95% CIs.

Table 1

All-cause SMRs for people diagnosed with SMI by sex and age group in combined cohort.

Diagnostic group ^a	No. of deaths	SMR						
		(95% CI)						
		Age (years)						
		Overall	Male	Female	<45	45–64	65–84	≥85
All severe mental illness	4709	2.6 (2.5–2.6)	3.0 (2.9–3.2)	2.3 (2.3–2.4)	5.8 (5.3–6.4)	3.3 (3.1–3.5)	2.4 (2.3–2.5)	2.0 (1.9–2.1)
Schizophrenia, Schizotypal & delusional disorders	2681	2.7 (2.6–2.8)	3.3 (3.1–3.5)	2.3 (2.2–2.5)	6.8 (6.1–7.5)	3.8 (3.5–4.1)	2.5 (2.3–2.6)	1.8 (1.6–1.9)
Bipolar disorder & other mood related disorders	1565	2.2 (2.1–2.3)	2.4 (2.2–2.6)	2.1 (2.0–2.3)	4.1 (3.4–4.9)	2.8 (2.5–3.1)	2.0 (1.9–2.1)	1.6 (1.5–1.9)
Other non-organic psychotic disorders	654	3.2 (2.9–3.4)	3.8 (3.3–4.2)	2.9 (2.7–3.2)	5.1 (3.5–7.8)	2.3 (1.7–3.1)	3.7 (3.3–4.2)	2.8 (2.5–3.1)

^a Refer to Supplementary Table 1 for the diagnoses included in each diagnostic group.

and cancers (61.8%). Diseases of the circulatory system alone accounted for 28.4% (1339/4709) of all deaths; with ischaemic heart disease being the most common. Deaths from respiratory diseases accounted for 17.8% of deaths (840/4709); with just under half attributable to pneumonia alone (418/840). Cancers accounted for 15.6% (735/4709) of all deaths; the most common being lung and gastrointestinal cancer. 9.3% (440/4709) of deaths were due to suicides (self-harm and events of undetermined intent) and accidents. Deaths attributed to Alzheimer's, senility and dementia taken together across ICD-10 categories accounted for 11.8% (555/4709) of deaths.

Overall SMRs associated with specific cause of deaths examined in the present study for the combined cohort are displayed in Table 2

and SMRs for males, female and age groups are summarised in Table 3. SMRs associated with unnatural causes (SMR: 6.9; 95% CI: 6.2–7.5) were higher than with natural causes (SMR: 2.4; 95% CI: 2.3–2.5, see Table 2). In particular, males tended to have higher SMRs than females for unnatural causes of death (males: SMR: 7.3; 95% CI: 6.4–8.1; females: SMR: 5.9; 95% CI: 5.0–6.8, Table 3). The highest cause-specific SMR was for ill-defined or unknown causes (SMR: 13.3; 95% CI: 10.1–17.2) followed by suicide and events of undetermined intent (SMR: 12.1; 95% CI: 10.6–13.8). The SMR for the latter was especially elevated in females (SMR: 21.4; 95% CI: 17.1–26.4). We further compared suicide in the secondary care cohort with the primary care cohort. The SMR for suicide for the secondary care cohort was considerably

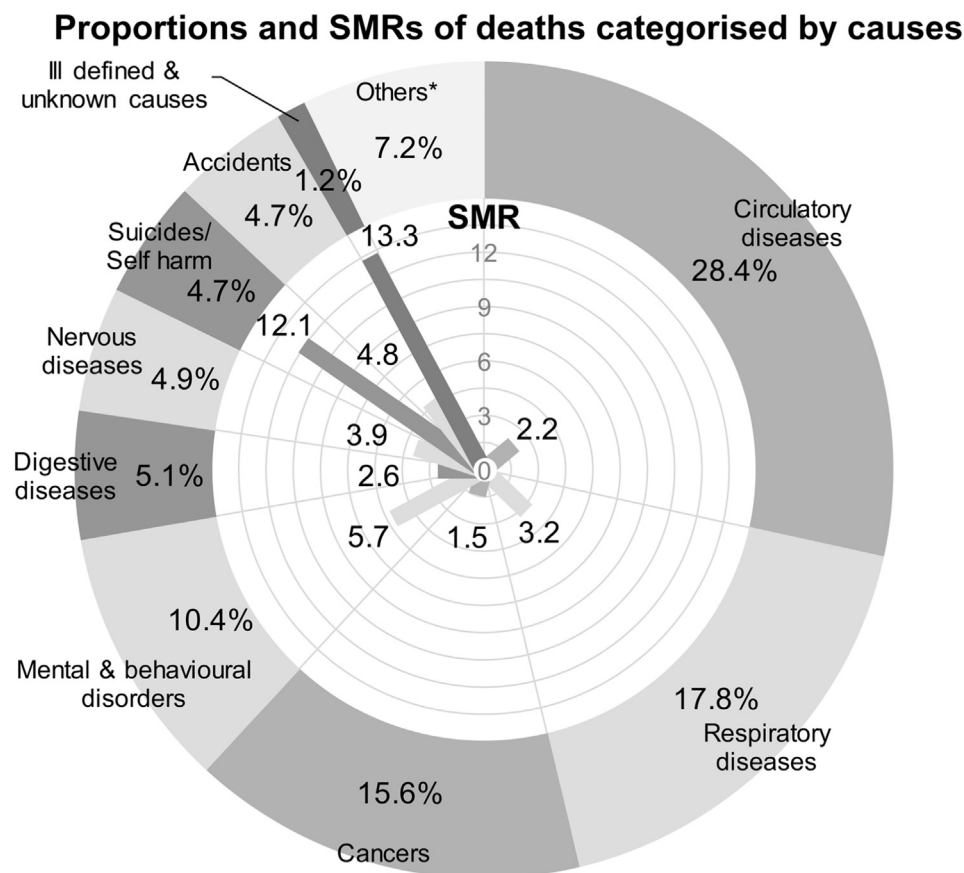


Fig. 2. Proportion of deaths by underlying causes (the outermost ring) and the corresponding SMR (polar bar chart with labelled values) in persons diagnosed with SMI in the combined cohort. * "Others" includes genitourinary, symptoms, signs and abnormal clinical findings (except ill-defined and unknown causes), infections, endocrine, nutritional and metabolic diseases plus a small number of other rarer causes. Note that SMR for "Others" are not shown for clarity. Reader may refer to Table 3 for the relevant values.

Table 2

Cause-specific SMRs for people diagnosed with SMI in the combined cohort.

Category	Sub-category	SMR (95% CI)	Category	Sub-category	SMR (95% CI)
All causes		2.6 (2.5–2.6)	Diseases of the digestive system		2.6 (2.2–2.9)
	Unnatural	6.9 (6.2–7.5)		Liver disease	2.5 (2.0–3.2)
	Natural	2.4 (2.3–2.5)		Other diseases of intestine & peritoneum	2.8 (1.8–4.1)
Diseases of the circulatory system		2.2 (2.0–2.3)	Diseases of the nervous system		3.9 (3.5–4.5)
	Ischaemic heart disease	2.0 (1.8–2.1)		Parkinson's disease	5.4 (4.3–6.7)
	Cerebrovascular disease	2.3 (2.1–2.6)		Alzheimer's disease	3.8 (3.0–4.6)
	Other cerebrovascular diseases	2.3 (2.0–2.6)		Other diseases of the nervous system	2.8 (2.1–3.9)
	Other circulatory diseases	2.3 (1.9–2.8)	Symptoms, signs & abnormal clinical findings		3.5 (2.9–4.3)
Neoplasms		1.5 (1.4–1.6)		Senility	2.1 (1.6–2.7)
	Gastrointestinal cancer	1.3 (1.2–1.5)		Ill-defined & unknown causes	13.3 (10.1–17.2)
	Lung cancer	1.7 (1.4–1.9)	Endocrine, nutritional & metabolic disease		2.2 (1.7–2.8)
Diseases of the respiratory system		3.2 (3.0–3.4)		Diabetes	1.8 (1.3–2.4)
	Pneumonia	3.8 (3.5–4.2)	Infections & parasitic diseases		2.6 (2.0–3.4)
	COPD	2.5 (2.2–2.9)		Septicaemia	3.0 (2.0–4.1)
	Other respiratory diseases	1.8 (1.2–2.6)		Intestinal infections due to specified organisms	1.8 (1.0–3.0)
Mental & Behavioural disorders		5.7 (5.2–6.2)	Diseases of the genitourinary system		2.8 (2.3–3.4)
	Dementia	5.2 (4.7–5.7)		Glomerular & renal tubulo-interstitial disease	4.9 (3.1–7.6)
	Substance abuse	8.2 (5.8–11.3)		Renal failure	1.6 (1.0–2.5)
Diseases of the digestive system		2.6 (2.2–2.9)	Accidents (unintentional injuries)		4.8 (4.2–5.4)
	Peptic ulcer	2.4 (1.5–3.6)	Suicide, self-harm & undetermined intent		12.1 (10.6–13.8)

higher (SMR: 16.5; 95% CI: 14.1–19.1) than for the primary care cohort (SMR: 8.9; 95% CI: 7.4–10.6) when compared to the general population.

For natural causes, we found the highest differences in mortality to be deaths from Parkinson's (SMR: 5.4; 95% CI: 4.3–6.7). A cluster of cognitive decline related deaths was also particularly elevated in comparison to the general population: dementia (SMR: 5.2; 95% CI 4.7–5.7); Alzheimer's (SMR: 3.8; 95% CI: 3.0–4.6); and senility (SMR: 2.1; 95% CI: 1.6–2.7). The ratio of deaths from respiratory diseases was found to be high (SMR: 3.2; 95% CI: 3.0–3.4), particularly pneumonia (SMR: 3.8; 95% CI: 3.5–4.2). We also found the ratio of deaths from genitourinary causes to be elevated (SMR: 2.8; 95% CI: 2.3–3.4). The ratios of deaths attributable to diseases of the circulatory system (SMR: 2.2; 95% CI: 2.0–2.3), including cerebrovascular disease (SMR: 2.3; 95% CI 2.1–2.6) and ischaemic heart disease (SMR: 2.0; 95% CI: 1.8–2.1), were doubled compared to the general population. Deaths from diseases of the digestive system (SMR: 2.6; 95% CI: 2.2–2.9) and diabetes related deaths (SMR: 2.2; 95% CI: 1.7–2.8) were elevated. We found little difference in mortality from cancers/neoplasms (SMR: 1.5; 95% CI: 1.4–1.6).

4. Discussion

We present what is to our knowledge the first study to assess mortality in people with SMI drawn from both hospital inpatient and primary care records in a linked dataset. We have been able to identify an ascertainment bias in previous mortality studies where patient inclusion was based on hospitalisation alone (Hoang et al., 2011) or out-patient and hospitalised secondary care cohorts (Jayatilleke et al.,

2017), or primary care records alone (Hayes et al., 2017; Osborn et al., 2007). SMRs for people with SMI identified from hospital inpatient settings were more elevated than those identified in a primary care setting or a combination of both. The higher SMRs observed from the secondary care cohort might be due to either shorter duration of follow-up periods i.e., participants died sooner, or differences in disease severity between the primary and secondary care cohorts. SMRs for participants in the primary care cohort who were hospitalised were no different to those not hospitalised (the latter includes those seen in out-patients). This does not support the assumption of difference in disease severity between cohorts. It may reflect those within the secondary care cohort who do not access primary care but are admitted through emergency departments. It may also reflect differential ages between the cohorts with older members of the hospitalised cohort more likely to have late-onset psychotic disorders with potentially different aetiologies.

For all-cause mortality across data sources, our results were similar to those reported in studies from secondary care settings. We found people with SMI had a two to threefold higher death rate than the general population. SMRs for individuals with schizophrenia related disorders were higher than those with bipolar disorders. We also found the mortality gap tended to decrease with age for all causes of death examined in the present study except for cerebrovascular disease and mental behavioural disorders (dementia and substance misuse). This age-dependent decrease in mortality has also been reported elsewhere (Termorshuizen et al., 2013).

Using a similar categorisation strategy adopted in a previous study (Termorshuizen et al., 2013), we computed SMRs associated with both

Table 3
SMRs for cause-specific mortality in SMI stratified by gender and age.

		SMR (95% CI)				Age (years)			
		No. of deaths	Overall	Male	Female	<45	45–64	65–84	≥85
All causes		4709	2.6 (2.5–2.6)	3.0 (2.9–3.2)	2.3 (2.3–2.4)	5.8 (5.3–6.4)	3.3 (3.1–3.5)	2.4 (2.3–2.5)	2.0 (1.9–2.1)
	Unnatural	441	6.9 (6.2–7.5)	7.3 (6.4–8.1)	5.9 (5.0–6.8)	10.0 (8.7–11.4)	9.9 (8.4–11.6)	3.5 (2.7–4.5)	2.3 (1.6–3.3)
	Natural	4257	2.4 (2.3–2.5)	2.8 (2.7–2.9)	2.3 (2.2–2.3)	4.3 (3.7–4.8)	3.0 (2.8–3.2)	2.4 (2.3–2.5)	2.0 (1.8–2.1)
Circulatory diseases		1339	2.2 (2.0–2.3)	2.5 (2.3–2.8)	2.0 (1.9–2.1)	3.7 (2.8–4.9)	3.4 (3.0–3.8)	2.2 (2.0–2.3)	1.5 (1.4–1.7)
	Ischaemic heart disease	585	2.0 (1.8–2.1)	2.5 (2.2–2.7)	1.7 (1.5–2.0)	3.7 (2.4–5.4)	2.9 (2.5–3.5)	2.0 (1.7–2.2)	1.4 (1.1–1.7)
	Cerebrovascular disease	390	2.3 (2.1–2.6)	2.7 (2.3–3.2)	2.2 (1.9–2.5)	0.8 (0.1–2.6)	3.6 (2.7–4.7)	2.6 (2.2–2.9)	1.9 (1.6–2.3)
	Other cerebrovascular	258	2.3 (2.0–2.6)	2.8 (2.3–3.4)	2.1 (1.8–2.4)	5.3 (3.2–8.3)	5.0 (3.8–6.4)	2.3 (1.9–2.7)	1.4 (1.1–1.8)
	Other circulatory	106	2.3 (1.9–2.8)	2.1 (1.6–2.9)	2.3 (1.8–2.9)	6.0 (2.6–11.9)	3.6 (2.3–5.3)	2.1 (1.7–2.7)	1.1 (0.6–1.8)
Neoplasms		735	1.5 (1.4–1.6)	1.7 (1.5–1.8)	1.4 (1.3–1.6)	2.0 (1.5–2.7)	1.6 (1.4–1.9)	1.4 (1.3–1.5)	1.3 (1.1–1.6)
	Gastrointestinal cancer	188	1.3 (1.2–1.5)	1.4 (1.1–1.7)	1.4 (1.1–1.7)	0.8 (0.2–2.2)	1.5 (1.1–1.9)	1.3 (1.1–1.6)	1.2 (0.8–1.8)
	Lung cancer	176	1.7 (1.4–1.9)	1.9 (1.5–2.3)	1.6 (1.3–2.0)	4.7 (2.2–8.9)	1.7 (1.3–2.3)	1.5 (1.2–1.8)	2.0 (1.2–3.2)
Respiratory diseases		840	3.2 (3.0–3.4)	3.9 (3.5–4.4)	3.0 (2.7–3.3)	10.4 (7.2–14.6)	6.2 (5.3–7.2)	3.4 (3.1–3.7)	2.1 (1.8–2.4)
	Pneumonia	418	3.8 (3.5–4.2)	5.2 (4.4–6.0)	3.3 (2.9–3.7)	10.7 (5.9–17.8)	9.1 (6.9–11.9)	5.1 (4.4–5.8)	2.2 (1.8–2.6)
	COPD	233	2.5 (2.2–2.9)	3.1 (2.5–3.7)	2.3 (1.9–2.8)	15.9 (6.9–31.4)	5.7 (4.5–7.1)	2.2 (1.8–2.6)	1.2 (0.8–1.8)
	Other respiratory diseases	28	1.8 (1.2–2.6)	1.7 (0.9–2.8)	2.3 (1.4–3.7)	15.6 (5.0–37.7)	2.5 (1.0–5.2)	1.6 (0.9–2.5)	0.9 (0.1–2.8)
Mental & behavioural disorders		489	5.7 (5.2–6.2)	7.6 (6.5–8.9)	4.9 (4.4–5.5)	9.5 (6.4–13.6)	11.2 (7.5–16.1)	6.3 (5.5–7.2)	4.7 (4.1–5.3)
	Dementia	417	5.2 (4.7–5.7)	6.9 (5.7–8.2)	4.6 (4.1–5.1)	0.0 (0.0–0.0)	10.2 (5.2–18.3)	5.8 (5.0–6.6)	4.6 (4.0–5.2)
	Substance abuse	35	8.2 (5.8–11.3)	8.3 (5.7–11.6)	5.4 (2.0–12.0)	9.3 (6.1–13.5)	5.5 (2.4–10.9)	10.6 (2.7–29.0)	0.0 (0.0–0.0)
Digestive system diseases		239	2.6 (2.2–2.9)	3.3 (2.8–3.9)	2.0 (1.6–2.4)	4.5 (3.3–6.1)	3.2 (2.6–4.0)	2.2 (1.8–2.7)	1.4 (1.0–2.1)
	Other diseases of intestine & peritoneum	24	2.8 (1.8–4.1)	4.2 (2.1–7.4)	2.2 (1.2–3.6)	12.2 (2.0–40.2)	5.1 (2.1–10.7)	1.9 (1.0–3.4)	2.9 (1.2–6.1)
	Peptic ulcer	21	2.4 (1.5–3.6)	2.3 (1.1–4.4)	2.5 (1.4–4.2)	3.8 (0.2–18.9)	1.9 (0.5–5.0)	2.8 (1.6–4.7)	1.5 (0.4–4.0)
	Liver disease	78	2.5 (2.0–3.2)	3.0 (2.3–3.9)	1.9 (1.2–2.8)	3.9 (2.6–5.5)	2.4 (1.7–3.2)	1.6 (0.9–2.9)	2.1 (0.1–10.1)
Nervous system diseases		233	3.9 (3.5–4.5)	5.5 (4.5–6.5)	3.2 (2.6–3.8)	2.6 (1.2–5.0)	4.6 (3.4–6.3)	4.4 (3.7–5.2)	3.0 (2.3–4.0)
	Parkinson's	77	5.4 (4.3–6.7)	8.3 (6.2–10.9)	3.9 (2.7–5.6)	126.6 (6.3–624.3)	15.3 (5.6–33.8)	5.7 (4.3–7.3)	3.6 (2.0–5.9)
	Alzheimer's	85	3.8 (3.0–4.6)	6.0 (4.1–8.5)	3.0 (2.3–3.9)	0.0 (0.0–0.0)	1.5 (0.1–7.2)	4.8 (3.6–6.2)	2.8 (1.9–4.0)
	Other diseases of the nervous system	39	2.8 (2.1–3.9)	3.6 (2.3–5.3)	2.3 (1.4–3.7)	4.0 (1.3–9.6)	4.1 (2.5–6.4)	2.2 (1.3–3.5)	1.8 (0.5–4.9)
Signs, symptoms & abnormal clinical findings		109	3.5 (2.9–4.3)	7.9 (5.8–10.4)	2.4 (1.9–3.1)	17.2 (11.8–24.3)	11.1 (7.0–16.9)	3.3 (1.8–5.5)	2.0 (1.5–2.6)
Ill-defined & unknown causes		55	13.3 (10.1–17.2)	14.0 (9.9–19.2)	11.8 (7.4–18.0)	17.7 (12.1–25.1)	12.2 (7.6–18.5)	7.1 (2.6–15.7)	6.6 (0.3–32.7)
	Senility	53	2.1 (1.6–2.7)	3.3 (1.7–5.9)	1.8 (1.4–2.5)	– ^a	– ^a	2.8 (1.3–5.2)	2.0 (1.5–2.7)
Endocrine, nutritional & metabolic diseases		59	2.2 (1.7–2.8)	2.9 (1.9–4.1)	1.8 (1.3–2.6)	4.9 (2.3–9.3)	4.7 (2.9–7.2)	1.6 (1.1–2.4)	1.3 (0.6–2.3)
	Diabetes	36	1.8 (1.3–2.4)	2.4 (1.5–3.7)	1.4 (0.9–2.2)	2.9 (0.5–9.7)	4.5 (2.4–7.7)	1.3 (0.7–2.1)	1.3 (0.6–2.5)
Infections & parasitic diseases		61	2.6 (2.0–3.4)	2.8 (1.8–4.3)	2.6 (1.9–3.5)	6.7 (2.5–15.0)	4.5 (2.5–7.5)	2.6 (1.8–3.7)	1.5 (0.8–2.6)
	Septicaemia	31	3.0 (2.0–4.1)	3.3 (1.7–5.7)	2.8 (1.8–4.3)	9.8 (2.5–26.6)	3.3 (1.0–7.9)	3.2 (1.9–4.9)	1.8 (0.7–3.8)
	Intestinal infections due to specified organisms	14	1.8 (1.0–3.0)	2.0 (0.6–4.8)	1.7 (0.9–3.1)	0.0 (0.0–0.0)	4.9 (0.8–16.2)	1.9 (0.9–3.7)	1.3 (0.4–3.1)
Genitourinary diseases		112	2.8 (2.3–3.4)	3.0 (2.1–4.1)	2.8 (2.2–3.5)	0.0 (0.0–0.0)	4.0 (2.0–7.1)	3.4 (2.6–4.3)	2.2 (1.6–3.0)
	Glomerular & renal tubulo-interstitial diseases	19	4.9 (3.1–7.6)	8.7 (4.6–15.1)	3.2 (1.5–6.0)	0.0 (0.0–0.0)	4.7 (0.8–15.4)	5.5 (2.9–9.5)	4.8 (2.0–10.1)
	Renal failure	20	1.6 (1.0–2.5)	1.4 (0.6–3.0)	1.8 (1.0–3.0)	0.0 (0.0–0.0)	3.7 (0.9–10.0)	1.2 (0.5–2.3)	1.9 (1.0–3.4)
Accidents (unintentional injuries)		219	4.8 (4.2–5.4)	6.1 (5.1–7.1)	3.3 (2.6–4.1)	8.1 (6.6–9.9)	8.2 (6.4–10.4)	2.4 (1.7–3.3)	2.2 (1.5–3.2)
Suicide, self-harm & undetermined intent		221	12.1 (10.6–13.8)	9.2 (7.7–10.8)	21.4 (17.1–26.4)	12.4 (10.3–14.7)	12.1 (9.6–15.1)	12.1 (7.9–17.9)	3.7 (0.2–18.5)

^a SMR is not available for expected death equals to zero.

natural and unnatural causes of death. SMRs associated with unnatural causes of death were found to be higher than those associated with natural ones and higher in males than in females. However, SMRs specifically associated with suicide, self-harm and undetermined intent were higher in females.

In addition to all-cause mortality, we also report on a broad array of underlying causes of death in those with SMI using a cohort sourced from a combination of primary and secondary care settings. Some of these causes are not commonly described elsewhere. In those with SMI the highest SMRs were found from ill-defined and unknown causes of death, suicide and substance abuse. Ill-defined and unknown causes are often misclassifications of death from ischaemic heart disease and suicide (Lozano et al., 2001; Ohberg and Lonnqvist, 1998). Deaths from cardiac arrhythmias are not detectable even at autopsy. Suicide may also be misclassified due to the additional burden of proof i.e., beyond reasonable doubt at the coroner's court. Previous studies

have shown that causes of death from ill-defined and unknown causes are more common in marginal populations, specifically the homeless and the elderly living alone, but this is likely to also apply to those with SMI (Andreev et al., 2008).

The lifetime risk of suicide for this population has been estimated to be between 5%–13% (Hor and Taylor, 2010; Osborn et al., 2007; Pompili et al., 2007). We found the suicide ratios for this population to be disturbingly high, particularly for females. Death from suicide is three times higher for males than females in the general population. However, this disparity in rates does not follow for females with SMI. The psychosis may diminish any inhibition to suicide that is present in women generally (Caldwell and Gottesman, 1990). We found that the SMR for suicide was considerably higher in the cohort drawn from the hospital inpatient setting than in the primary care sourced cohort. This is most likely due to the difference in levels of severity between the cohorts. This finding confirms previous studies in which suicide risk is highly

associated with psychiatric hospitalisations. Approximately a third of the suicides in people with schizophrenia occur during admission or the first week after discharge (Nordentoft et al., 2013). SMRs due to psychoactive substance abuse were unsurprisingly high in this population when compared to the general population. In a UK study, 44% of community mental health patients had reported problem drug use or harmful alcohol use in the previous year (Weaver et al., 2003).

SMRs associated with age-related cognitive decline diseases, such as dementia and Alzheimer's were found to be particularly elevated. It is possible that cognitive decline in schizophrenia may be misattributed to dementia or it may be that those already in contact with psychiatric services are more likely to be appropriately diagnosed than the general population. Mortality ratios from pathogenic agents, including microorganisms leading to death from septicaemia and intestinal and peritoneal infections and peptic ulcers were also very high. The elevated risk for this population of developing peptic ulcers has been reported elsewhere (Liao et al., 2014). It may be that symptoms are under-reported or under-diagnosed by those with SMI so they present late to services. However, immune system dysfunction and the involvement of infectious agents in the pathophysiology of these psychiatric diseases, including antimicrobial defence, are being reported (Yolken et al., 2016).

SMRs for respiratory diseases were also very high in comparison to the general population, particularly pneumonia. This can be perhaps explained by higher rates of smoking in this population (Olfson et al., 2015). We found a two and a half fold increased risk of death from cardiovascular disease in people with SMI, but this was lower than SMRs in neurological disorders, cognitive decline, infections and respiratory diseases. Despite this, given that cardiovascular disease is the most common cause of death in both general and the SMI populations in Western countries, much of the excess mortality in people with SMI will be attributable to this disease group (Osborn et al., 2007; Osborn et al., 2006). Similarly, we found death rates from cancers, which although slightly elevated, did not result in the highest disparities compared to the general population, which is in keeping with findings from many other studies (Kisely et al., 2013; Osborn et al., 2007).

4.1. Strengths and limitations

We believe this is the first study to evaluate mortality for people with SMI drawn from both primary care and secondary inpatient care settings in linked data. This population-wide observational study thus encompasses the spectrum of severity of SMI of those engaged with services. However, some vulnerable groups, e.g., the homeless, may not be registered with a GP and would not be included. The combination of both settings balances some of the weaknesses of each alone. However, potential confounders may be that if an individual has a physical disorder and visits a GP they may be more likely to receive an SMI diagnosis. Two previous studies have made direct comparisons of mortality risks between inpatient and outpatients for this population to establish the over-estimation (Amaddeo et al., 1995; Crump et al., 2013) when compared to studies based solely on in-patients (Hoang et al., 2011). Ideally, we would have included those with SMI seen in out-patients. However in the United Kingdom, diagnostic coding (rather than specialty coding) in the out-patient dataset is too poor to utilise in studies of this type. Letters received from out-patients are Read coded in the primary care dataset. The diagnostic codes to create our cohorts have been previously validated (Economou et al., 2012; Lloyd et al., 2015).

A further strength is that we have coverage of deaths for the whole general population. It is unclear, but likely, in other similar studies conducted in the UK that the linkage of the mortality dataset is to a subset of the population. If our study had been restricted to those present in the hospital episode statistics/admissions dataset with or without SMI, only 54.9% of those with an SMI diagnosis in the combined cohort would have been linked to the mortality dataset (16,371/29,797). Similarly most primary care databases are sampled i.e., studies based in The Health Improvement Network (Hayes et al., 2017), cover a sampled

population of 6% of the United Kingdom population, whereas SAIL provides population level data of 74% of the Wales population allowing whole general population linkage of mortality. Also by calculating SMRs for underlying cause of death using the expected rates from the specific corresponding causes in the general population of Wales, we believe that the relative excess can be accurately determined.

A further advantage is that we have included some underlying causes of death rarely reported elsewhere, for example, Hayes et al. (2017) report mortality from all causes, cardiovascular disorders and suicide only. Similarly in a study based in a large secondary care database in London, reduced life expectancy in those with SMI was accounted for by a wide range of major grouped causes of death but these were limited to circulatory, cancer, respiratory, digestive, suicide, other external and all other causes (Jayatilke et al., 2017). Larger cohorts may identify further causes yielding even higher rates, e.g., epilepsy. We were restricted by the size of the cohort as to how many specific causes we could reasonably include. Other limitations include the usual caveats of the use of routine data (not collected primarily for research purposes, quality and completeness issues) and accuracy of death certification, particularly for suicide (Gunnell et al., 2011).

Indirect standardisation was used for the calculation of SMRs, which means we cannot quantify the differences in premature mortality between our specified cohorts; only in relation to the general population since population structures within each cohort may vary.

Some authors argue that life expectancy is a preferable measure of mortality to the SMR (Jayatilke et al., 2017), primarily since it is easier to interpret and communicate, particularly for laypeople and clinicians working outside of academia. However, computation of this statistic has a number of difficulties. For example, its reliance on the construction of current life-tables makes it impractical for routine use, while for small populations computation of life expectancy may not be possible at all (Silcocks et al., 2001; Tsai et al., 1992).

4.2. Implications for policy, practice and future research

Methodological considerations and comprehensive characterisations of mortality in this patient population are important when informing policy initiatives that improve services and target interventions. By including people from both primary and secondary care in this study we highlight the need for better integration not only between specialty teams within hospitals, but also between primary and secondary care, particularly since secondary care mental health services are under increasing pressure to discharge people back to primary care earlier (Rethink Mental Illness, 2012). Therefore, the development of policies to: expand the remit of liaison psychiatry services from exclusively hospital based into community settings (Department of Health, 2014); further develop health promotion interventions for unhealthy lifestyle behaviours; and improve screening opportunities for early detection and intervention is welcomed. It may be worth reflecting on investing, targeting and delivering lifestyle interventions to improve physical health care for people with SMI in secondary care settings, which is currently poor (Bailey et al., 2012; Crawford et al., 2014; Royal College of Psychiatrists, 2015).

Previous studies may have over- or under-estimated premature mortality in people with SMI to some extent but, as we have demonstrated, SMRs are raised in all settings by an unacceptable ratio. Therefore previous literature has had appropriate major policy implications for improving the physical health of people with SMI. The significant emphasis on improving physical health care for people with SMI through screening for cardiovascular and metabolic disorders is important to address this health injustice, but our study suggests this could be broadened to, for example, peptic ulcers and early recognition and treatment of infection.

Our results demonstrate that suicide prevention in this population is an important and appropriate focus of national policy. However, a greater emphasis on suicide prevention in community settings in this

group should be considered. Suicide rates under crisis resolution and home treatment teams were found to be higher (14.6 per 10,000 episodes) than that under psychiatric hospital admission (8.8 per 10,000 admission) in a recent report (Hunt et al., 2014).

Future studies should explore premature mortality in those with SMI using both primary and secondary care sources of cases. This includes whether the all-cause mortality gap has increased differentially over the last decade in those with hospital admissions compared to that demonstrated in primary care data (Hayes et al., 2017). Studies from secondary care demonstrate the excess mortality persists, but more recent comprehensive studies are essential (Chang et al., 2011). Long term studies are also needed to determine the extent and interaction between antipsychotic treatment, metabolic indicators, lifestyle choices, social deprivation, age and genetics that lead to premature mortality, particularly from certain diseases. In our whole population-based study we found some of the highest mortality ratios in causes not often commonly described elsewhere, such as deaths from unexplained causes, neurological disorders, cognitive decline, infections and respiratory diseases.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2018.04.009>.

References

- Amadeo, F., Bisoffi, G., Bonizzato, P., Micciolo, R., Tansella, M., 1995. Mortality among patients with psychiatric illness. A ten-year case register study in an area with a community-based system of care. *Br. J. Psychiatry* 166 (6), 783–788.
- Andreev, E., Pridemore, W.A., Shkolnikov, V.M., Antonova, O.I., 2008. An investigation of the growing number of deaths of unidentified people in Russia. *Eur. J. Pub. Health* 18 (3), 252–257.
- Appleby, L., Shaw, J., Sherratt, J., Amos, T., Robinson, J., McDonnell, R., 2001. Safety first: a Five-year report of the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness. Report for the Department of Health.
- Bailey, S., Gerada, C., Lester, H., Shiers, D., 2012. The cardiovascular health of young people with severe mental illness: addressing an epidemic within an epidemic. *The Psychiatrist Online* 36 (10), 375–378.
- Brown, S., Inskip, H., Barraclough, B., 2000. Causes of the excess mortality of schizophrenia. *Br. J. Psychiatry* 177 (3), 212–217.
- Bushe, C.J., Taylor, M., Haukka, J., 2010. Mortality in schizophrenia: a measurable clinical endpoint. *J. Psychopharmacol.* 24 (11), 17–25.
- Copeland, L.A., Zeber, J.E., Wang, C.-P., Parchman, M.L., Lawrence, V.A., Valenstein, M., Miller, A.L., 2009. Patterns of primary care and mortality among patients with schizophrenia or diabetes: a cluster analysis approach to the retrospective study of healthcare utilization. *BMC Health Serv. Res.* 9 (1), 127.
- Carney, C.P., Jones, L., Woolson, R.F., 2006. Medical comorbidity in women and men with schizophrenia: a population-based controlled study. *J. Gen. Intern. Med.* 21 (11), 1133–1137.
- Caldwell, C.B., Gottesman, I.I., 1990. Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophr. Bull.* 16 (4), 571–589.
- Chang, C.K., Hayes, R.D., Perera, G., Broadbent, M.T.M., Fernandes, A.C., Lee, W.E., Hotopf, M., Stewart, R., 2011. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. *PLoS One* 6 (5), e19590.
- Correll, C.U., Ng-Mak, D.S., Stafkey-Mailey, D., Farrelly, E., Rajagopalan, K., Loebel, A., 2017. Cardiometabolic comorbidities, readmission, and costs in schizophrenia and bipolar disorder: a real-world analysis. *Ann. General Psychiatry* 16 (1), 9.
- Crawford, M.J., Jayakumar, S., Lemmey, S.J., Zalewska, K., Patel, M.X., Cooper, S.J., Shiers, D., 2014. Assessment and treatment of physical health problems among people with schizophrenia: national cross-sectional study. *Br. J. Psychiatry* 205 (6), 473–477.
- Crump, C., Ioannidis, J.P.A., Sundquist, K., Winkleby, M.A., Sundquist, J., 2013. Mortality in persons with mental disorders is substantially overestimated using inpatient psychiatric diagnoses. *J. Psychiatr. Res.* 47 (10), 1298–1303.
- Department of Health, 2014. Closing the gap: priorities for essential change in mental health. Report for the Department of Health.
- Economou, A., Grey, M., McGregor, J., Craddock, N., Lyons, R.A., Owen, M.J., Price, V., Thomson, S., Walters, J.T.R., Lloyd, K., 2012. The Health Informatics Cohort Enhancement project (HICE): using routinely collected primary care data to identify people with a lifetime diagnosis of psychotic disorder. *BMC Res. Notes* 5 (1), e95.
- Ford, D.V., Jones, K.H., Verplanck, J.-P., Lyons, R.A., John, G., Brown, G., Brooks, C.J., Thompson, S., Bodger, O., Couch, T., Leake, K., 2009. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv. Res.* 9 (1), 157.
- Gunnell, D., Hawton, K., Kapur, N., 2011. Coroners' verdicts and suicide statistics in England and Wales. *BMJ* 343, d6030.
- Hayes, J.F., Marston, L., Walters, K., King, M.B., Osborn, D.P.J., 2017. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. *Br. J. Psychiatry* 211 (3), 175–181.
- Hoang, U., Stewart, R., Goldacre, M.J., 2011. Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999–2006. *BMJ* 343, d5422.
- Hor, K., Taylor, M., 2010. Suicide and schizophrenia: a systematic review of rates and risk factors. *J. Psychopharmacol.* 24 (11), 81–90.
- Hunt, I.M., Rahman, M.S., While, D., Windfuhr, K., Shaw, J., Appleby, L., Kapur, N., 2014. Safety of patients under the care of crisis resolution home treatment services in England: a retrospective analysis of suicide trends from 2003 to 2011. *Lancet Psychiatry* 1 (2), 135–141.
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010. IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr. Eval. Carcinog. Risks Hum. 94, 1–412.
- Jayatilake, N., Hayes, R.D., Dutta, R., Shetty, H., Hotopf, M., Chang, C.-K., Stewart, R., 2017. Contributions of specific causes of death to lost life expectancy in severe mental illness. *Eur. Psychiatry* 43, 109–115.
- Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62 (6), 617–627.
- Kisely, S., Crowe, E., Lawrence, D., 2013. Cancer-related mortality in people with mental illness. *JAMA Psychiat.* 70 (2), 209–217.
- Leucht, S., Burkard, T., Henderson, J., Maj, M., Sartorius, N., 2007. Physical illness and schizophrenia: a review of the literature. *Acta Psychiatr. Scand.* 116 (5), 317–333.
- Liao, C.H., Chang, C.S., Chang, S.N., Muo, C.H., Lane, H.Y., Sung, F.C., Kao, C.H., 2014. The association of peptic ulcer and schizophrenia: a population-based study. *J. Psychosom. Res.* 77 (6), 541–546.
- Lloyd, K., McGregor, J., John, A., Craddock, N., Walters, J.T., Linden, D., Jones, I., Bental, R., Lyons, R.A., Ford, D.V., Owen, M.J., 2015. A national population-based e-cohort of people with psychosis (PsyCymru) linking prospectively ascertained phenotypically rich and genetic data to routinely collected records: overview, recruitment and linkage. *Schizophr. Res.* 166 (1), 131–136.
- Lozano, R., Murray, C.J., Lopez, A.D., Satoh, T., 2001. Miscoding and misclassification of ischaemic heart disease mortality. Global Program on Evidence for Health Policy Discussion Paper.
- Lyons, R.A., Jones, K.H., John, G., Brooks, C.J., Verplanck, J.-P., Ford, D.V., Brown, G., Leake, K., 2009. The SAIL databank: linking multiple health and social care datasets. *BMC Med. Inform. Decis. Mak.* 9 (1), 3.
- McDermott, S., Moran, R., Platt, T., Isaac, T., Wood, H., Dasari, S., 2005. Heart disease, schizophrenia, and affective psychoses: epidemiology of risk in primary care. *Community Ment. Health J.* 41 (6), 747–755.
- Newcombe, R.G., 1998. Two-sided confidence intervals for the single proposition: comparison of seven methods. *Stat. Med.* 17 (8), 857–872.
- Nordentoft, M., Wahlbeck, K., Hällgren, J., Westman, J., Ösby, U., Alinaghizadeh, H., Gissler, M., Laursen, T.M., 2013. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS One* 8 (1), e51176.
- Ohberg, A., Lonnqvist, J., 1998. Suicides hidden among undetermined deaths. *Acta Psychiatr. Scand.* 98 (3), 214–218.
- Olsson, M., Gerhardt, T., Huang, C., Crystal, S., Stroup, T.S., 2015. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiat.* 72 (12), 1172–1181.
- Osborn, D.P.J., Nazareth, I., King, M.B., 2006. Risk for coronary heart disease in people with severe mental illness: cross-sectional comparative study in primary care. *Br. J. Psychiatry* 188 (3), 271–277.
- Osborn, D.P.J., Levy, G., Nazareth, I., Petersen, I., Islam, A., King, M.B., 2007. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's general practice research database. *Arch. Gen. Psychiatry* 64, 242.
- Pompili, M., Amador, X.F., Girardi, P., Harkavy-Friedman, J., Harrow, M., Kaplan, K., Krausz, M., Lester, D., Meltzer, H.Y., Modestini, J., Montross, L.P., Mortensen, P.B., Munk-Jørgensen, P., Nielsen, J., Nordentoft, M., Saarninen, P.I., Zisook, S., Wilson, S.T., Tatarelli, R., 2007. Suicide risk in schizophrenia: learning from the past to change the future. *Ann. General Psychiatry* 6, 10.
- Ressing, M., Blettner, M., Klug, S.J., 2010. Data analysis of epidemiological studies: part 11 of a series on evaluation of scientific publications. *Dtsch. Arztebl. Int.* 107, 187–192.
- Rethink Mental Illness, 2012. The Abandoned Illness: A Report by the Schizophrenia Commission.
- Rothman, K.J., Boice Jr., J.D., 1979. Epidemiologic Analysis With a Programmable Calculator. National Institute of Health, Washington, D.C.
- Royal College of Psychiatrists, 2015. National Audit of Schizophrenia. Royal College of Psychiatrists.
- Silcock, P.B.S., Jenner, D.A., Reza, R., 2001. Life expectancy as a summary of mortality in a population: statistical considerations and suitability for use by health authorities. *J. Epidemiol. Community Health* 55 (1), 38–43.
- Termorshuizen, F., Wierdsma, A.I., Smeets, H.M., Visser, E., Drukker, M., Nijman, H., Sytema, S., 2013. Cause-specific mortality among patients with psychosis: disentangling the effects of age and illness duration. *Psychosomatics* 54 (6), 536–545.
- Tsai, S.P., Hardy, R.J., Wen, C., 1992. The standardized mortality ratio and life expectancy. *Am. J. Epidemiol.* 135 (7), 824–831.
- Weaver, T., Madden, P., Charles, V., Stimson, G., Renton, A., Tyrer, P., Barnes, T., Bench, C., Middleton, H., Wright, N., Paterson, S., Shanahan, W., Seiwright, N., Ford, C., 2003. Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. *Br. J. Psychiatry* 183 (4), 304–313.

Volken, R., Adamos, M., Katsafanas, E., Khushalani, S., Origoni, A., Savage, C., Schweinfurth, L., Stallings, C., Sweeney, K., Dickerson, F., 2016. [Individuals hospitalized with acute mania have increased exposure to antimicrobial medications](#). *Bipolar Disord.* 18 (5), 404–409.